Remarks

This paper is filed in reply to the Official Action as described above. The Examiner has withdrawn claims 17 and 18 from consideration, and these claims have now been cancelled without prejudice. Claims 8 and 21-28 have been rejected. With this reply, claims 21-28 are cancelled without prejudice. Claim 8 remains pending in the case and is amended to better identify the subject matter claimed. Basis for the amendment introducing the terms "active against lepidopteran insects" can be found throughout the specification, and particularly in line one of paragraph [Para 82] on page 15 of the specification as filed. No new matter is introduced with this amendment. Claim 8 continues to be drawn to a protein corresponding to SEQ ID NO:4, first described by the applicant in the sequence listing and specification filed in December 2003, also referred to therein as TIC900.

The Examiner has objected to claims 21 – 28, and these claims have been cancelled from the present prosecution case, and without prejudice.

The Examiner cites Carozzi et al (US Patent 7,355,099 filed February 2003) as the basis for her rejection of claims 8 and 21-28 under 35 USC 103. The rejection of claims 21-28 is now moot as these claims have been cancelled. The reply to the rejection of claim 8 forms the basis for the balance of this paper.

The Carozzi et al priority document 60/448,810 (the '810 application) filed in February 2003 discloses a single nucleotide sequence SEQ ID NO 1 encoding a single protein SEQ ID NO 2 that exhibits a different amino acid sequence compared to SEQ ID NO:4 (TIC900) in the instant application. The '810 application discloses a protein (SEQ ID NO:2) that exhibits differences at no fewer than 6 amino acid residues compared to the corresponding residues in SEQ ID NO:4 (TIC900) in the instant application. The '810 application was not available as prior art until the corresponding US non-provisional application US 2004-0197916 A1 was published, October 7, 2004.

The non-provisional application filed by Carozzi et al that matured to US Patent No. 7,355,099 (the '099 patent) added matter to the priority document in the form of SEQ ID NO:5, because SEQ ID NO:5 is 28 amino terminal amino acid residues shorter than the protein set forth in the priority document as SEQ ID NO:2. SEQ ID NO:5 in the '099 patent also exhibits differences at no fewer than six (6) amino acid residues compared to the corresponding residues in SEQ ID NO:4 (TIC900) of the instant application. The applicant was thus first to disclose, and assertedly first to invent, the subject matter claimed in Claim 8 of the instant application. An interference proceeding established by the USPTO will be able to determine whether Carozzi et al or the instant applicants

were first to invent the subject matter of Claim 8 of the instant application.

As stated above, the Examiner relies upon the '099 patent in formulating her 35 USC 103 rejection of claim 8, and the '099 patent relies upon the '810 application for its claim to priority.

The Examiner continues to assert that it would have been obvious at the effective date of the instant application, two months prior to the filing date of the application later granted as the '099 patent which disclosed SEQ ID NO:5, to modify the amino acid sequence of SEQ ID NO:2 disclosed in the '810 application to arrive at the sequence of SEQ ID NO:4, which is the subject matter of the instant Claim 8. The Examiner asserts that the '810 application motivates the skilled artisan to make variants of SEQ ID NO:2 to arrive at the instantly claimed subject matter by making the 6 amino acid substitutions required to convert SEQ ID NO:2 of the '810 application into the instant SEQ ID NO:4, because the Examiner has indicated that the following amino acids in SEQ ID NO:4 represent a conservative substitution (amino acid 514), and substitutions suggested by Fig 1 of the cited reference at amino acids 175, 189, 391 and 537, or are a substitution at a site that appears to tolerate any type of amino acid (amino acid 145). This argument is traversed.

The '810 application teaches on page 13 of the specification at lines 7-13 that

> "the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences of the invention thereby leading to changes in the amino acid sequence of the encoded delta-endotoxin proteins, without altering the biological activity of the proteins.... such that one or more amino acid substitutions...are introduced into the encoded protein."

Additionally, the paragraph bridging pages 13 and 14 of the '810 application teaches

> "preferably, conservative amino acid substitutions may be made at one or more predicted, preferably nonessential amino acid residues...A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino a cids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycines, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta –branched side chains (e.g., threonine, valine, isoleucine), and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Such substitutions would not be made for conserved amino acid residues, or for amino acid residues residing within a conserved motif, where such residues are essential for protein activity."

The '810 application, and to the extent that the '099 patent is consistent, teach away from the subject matter that the Examiner asserts under the 35 USC 103 rejection of claim 8. To the extent that the '099 disclosure is different in view of the '810 application, the different subject matter in the

'099 patent would be unavailable as proper 35 USC 103 art in this matter.

At page 13 line 7 through page 14 line 2 of the '810 application, the skilled artisan is taught *to avoid* substitution of:

a glutamic acid (an acidic side chain) for a glycine residue (an uncharged polar side chain) at position 145,

a cysteine residue (an uncharged polar side chain) for an arginine (a basic side chain) at position 175,

a proline residue (a polar side chain) for a serine (an uncharged polar side chain) at position 391,

a glutamic acid residue (an acidic side chain) for a glutamine (an uncharged polar side chain) at position 514, or

a threonine residue (an uncharged polar side chain) for an alanine (a nonpolar side chain) at position 537.

SEQ ID NO:4 of the instant application in fact contains a glycine, an arginine, a serine, a glutamine, and an alanine at these requisite positions, and SEQ ID NO:2 of the cited reference contains a glutamate, a cysteine, a proline, a glutamate, and a threonine at these corresponding positions. Thus, the skilled artisan would have been led away from making the variant amino acid sequence set forth in SEQ ID NO:4 at the priority date of the cited reference.

The only residue that the '810 application teaches as a possible equivalent substitution from SEQ ID NO:2 of the '810 application to arrive at the corresponding position in SEQ ID NO:4 of the instant application would be an arginine (a basic side chain) for a lysine residue (also a basic side chain) at position 189.

In view of the alignment in the '810 application of the Cry1 proteins versus the protein as set forth in SEQ ID NO 2 (Figures 1 and 3), coupled with the disclosure of example 6 in the '810 application showing the very low percentage identity to other known delta-endotoxins, it is believed that the skilled artisan would not have made substitutions at the amino acid positions of the '810 application SEQ ID NO:2 protein as suggested by the Examiner to arrive at the instantly claimed protein set forth in SEQ ID NO:4, because the '810 application *teaches to avoid* making these particular substitutions and so there would have been no reasonable expectation of success with any such substitutions in view of the teaching in the '810 application. Furthermore, there was no teaching in the '810 application as to which if any amino acid substitution would be effective or detrimental to

the activity of the protein. The alignment of the protein set forth in SEQ ID NO:2 of the '810 application (SEQ ID NO:5 of the '099 patent) from amino acid position 29 through amino acid position 601 and the teaching of Example 6 therein show that there is greater dis-similarity between the protein of the '810 application and the aligned proteins than there is similarity . Thus, over the length of the 629 amino acids of the '810 application and the instant application proteins, the skilled artisan would have required undue experimentation to arrive at the protein of the present invention by mere substitution.

In view of the unpredictability of the substitutions, the dissimilarity of the proteins aligned to the '810 application protein, and the '810 application teaching away from substituting the amino acids at the indicated positions to arrive at the protein of the present invention, it is believed that the protein of the present invention would not have been obvious in view of the '810 application, or its subsequent non provisional application, the '099 patent. Therefore it is respectfully requested that the Examiner remove this grounds of rejection.

This paper is filed in response to the above captioned Official Action, along with a petition for an extension of time of five (5) months and the authorization for the Office to deduct the requisite fees for such petition and any other fees associated with this response from Applicant Monsanto Company's USPTO Deposit Account 13-4125. Therefore, it is believed that this paper is timely filed.

Claims 1-20 were originally filed. With this paper, originally filed claims 1-7, 9-16, and 19-20 are cancelled, claims 17-18 are withdrawn, new claims 21-28 are cancelled without prejudice, and claim 8 remains pending in the case.

Respectfully submitted,

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Date: _____

/ Timothy K. Ball /

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